02-19-02 FH 0300

TRANSMITTAL LETTER			Case No. 10466/201
Serial No. 09/990,438	Filing Date November 14, 2001	Examiner To be assigned	Group Art Unit 1646
Inventor(s) Ashkenazi et al.			
Title of Invention SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME			

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is Petition in Response to Notice of Omitted Item(s) in a Nonprovisional Application; pages 303-306 of specification; copy of return postcard; copy of Notice of Omitted Item(s) in a Nonprovisional Application; check in the amount of $130.00 and return postcard.

☐ Small entity status of this application under 37 CFR § 1.27 has been established by verified statement previously submitted.

☐ A verified statement to establish small entity status under 37 CFR §§ 1.9 and 1.27 is enclosed.

☐ Petition for a _____month extension of time.

☐ No additional fee is required.

☐ The fee has been calculated as shown below:

	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Small Entity Rate	Small Entity Add'l Fee	or	Other Than Small Entity Rate	Other Than Small Entity Add'l Fee
Total		Minus			x $9=			x $18=	
Indep.		Minus			x 42=			x $84=	
First Presentation of Multiple Dep. Claim					+$140=			+ $280=	
					Total add'l fee	$		Total add'l fee	$

☐ Please charge Deposit Account No. 23-1925 (BRINKS HOFER GILSON & LIONE) in the amount of $_____. A duplicate copy of this sheet is enclosed.

☒ A check in the amount of $130.00 to cover the filing fee is enclosed.

☒ The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 CFR § 1.16 and any patent application processing fees under 37 CFR § 1.17 associated with this communication or credit any overpayment to Deposit Account No. 23-1925. A duplicate copy of this sheet is enclosed.

☒ I hereby petition under 37 CFR § 1.136(a) for any extension of time required to ensure that this paper is timely filed. Please charge any associated fees which have not otherwise been paid to Deposit Account No. 23-1925. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Gregory M. Zinkl, Ph.D.
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I hereby certify that this correspondence is being deposited with the United States Postal Service as express mail, label no. EL448312405US with sufficient postage, in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on 2/15/02

Date: 2/15/02 Signature: _____

NEW CONTINUATION PATENT APPLICATION

In re Application of: Avi Ashkenazi et al.
Serial No.: To Be Assigned
Filed On: November 14, 2001
Mailed On: November 14, 2001

Docket No.: P2730P1C3
By: Elizabeth M. Barnes, Ph.D.
Reg. No.: 35,059

The following has been received in the U.S. Patent Office on the date stamped:

X Non-provisional application transmittal under 37 CFR 1.53 (b);
X Filing Fee ($) 710.00 (authorized to charge to Dep. Acct. 07-0630);
- 566 Pages of Specification
- 25 Pages of Claims
- 1 Page(s) of Abstract
- 330 Sheets of Drawings X Formal __ Informal

X Copy of executed Combined Declaration for Patent Application and Power of Atty. from parent application No. 09/941,992
X Paper and electronic copy of Sequence Listing
X Preliminary Amendment
X Associate Power of attorney
X Certificate of Express Mailing Express Mail Label No.: **EV 048 195 283 US**
X Postcard

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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/990,438	11/14/2001	Avi J. Ashkenazi	P2730P1C3

CONFIRMATION NO. 2374

FORMALITIES LETTER

OC000000007201361

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Date Mailed: 12/17/2001

NOTICE OF OMITTED ITEM(S) IN A NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

A filing date has been accorded to the above-identified nonprovisional application papers; however, the following item(s) appear to have been omitted from the application:

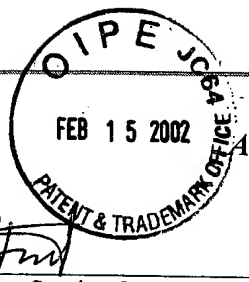
- Page(s) **303-306** of the specification (description and claims).

I. Should applicant contend that the above-noted omitted item(s) was in fact deposited in the U.S. Patent and Trademark Office (USPTO) with the nonprovisional application papers, a copy of this Notice and a petition (and $130.00 petition fee *(37 CFR 1.17(h))*) with evidence of such deposit **must** be filed within **TWO MONTHS** of the date of this Notice. The petition fee will be refunded if is determined that the item(s) was received by the USPTO.

II. Should applicant desire to supply the omitted item(s) and accept the date that such omitted item(s) was filed in the USPTO as the filing date of the above-identified application, a copy of this Notice, the omitted item(s) (with a supplemental oath or declaration in compliance with 37 CFR 1.63 and 1.64 referring to such items), and a petition under 37 CFR 1.182 (with the $130.00 petition fee *(37 CFR 1.17(h))* requesting the later filing date **must** be filed within **TWO MONTHS** of the date of this Notice.

III. The failure to file a petition (and petition fee) under the above options (I) or (II) within **TWO MONTHS** of the date of this Notice (37 CFR 1.181(f)) will be treated as a constructive acceptance by the applicant of the application as deposited in the USPTO. **THIS TWO MONTH PERIOD IS NOT EXTENDABLE UNDER 37 CFR 1.136(a) or (b)**. In the absence of a timely filed petition in reply to this Notice, the application will maintain a filing date as of the date of deposit of the application papers in the USPTO, and original application papers (*i.e.*, the original disclosure of the invention) will include only those application papers present in the USPTO on the date of deposit.

In the event that applicant elects not to take action pursuant to options (I) or (II) above (thereby constructively electing option (III)), amendment of the specification to renumber the pages consecutively and cancel incomplete sentences caused by any omitted page(s), and/or amendment of the specification to cancel all references to any omitted drawing(s), relabel the drawing figures to be numbered consecutively (if necessary), and correct the references in the specification to the drawing figures to correspond with any relabelled drawing figures, is required. Any drawing changes should be accompanied by a copy of the drawing figures showing the proposed changes in red ink. Such amendment and/or correction to the drawing figures, if necessary, should be by way of preliminary amendment submitted prior to the first Office action to avoid delays in the prosecution of the application.



A copy of this notice <u>MUST</u> be returned with the reply.

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Figure 304 shows the amino acid sequence (SEQ ID NO:422) derived from the coding sequence of SEQ ID NO:421 shown in Figure 303.

Figure 305 shows a nucleotide sequence (SEQ ID NO:423) of a native sequence PRO1384 (UNQ721) cDNA, wherein SEQ ID NO:423 is a clone designated herein as "DNA71159-1617".

Figure 306 shows the amino acid sequence (SEQ ID NO:424) derived from the coding sequence of SEQ ID NO:423 shown in Figure 305.

Figure 307 shows a nucleotide sequence (SEQ ID NO:494) of a native sequence PRO183 cDNA, wherein SEQ ID NO:494 is a clone designated herein as "DNA28498".

Figure 308 shows the amino acid sequence (SEQ ID NO:495) derived from the coding sequence of SEQ ID NO:494 shown in Figure 307.

Figure 309 shows a nucleotide sequence (SEQ ID NO:496) of a native sequence PRO184 cDNA, wherein SEQ ID NO:496 is a clone designated herein as "DNA28500".

Figure 310 shows the amino acid sequence (SEQ ID NO:497) derived from the coding sequence of SEQ ID NO:496 shown in Figure 309.

Figure 311 shows a nucleotide sequence (SEQ ID NO:498) of a native sequence PRO185 cDNA, wherein SEQ ID NO:498 is a clone designated herein as "DNA28503".

Figure 312 shows the amino acid sequence (SEQ ID NO:499) derived from the coding sequence of SEQ ID NO:498 shown in Figure 311.

Figure 313 shows a nucleotide sequence (SEQ ID NO:500) of a native sequence PRO331 cDNA, wherein SEQ ID NO:500 is a clone designated herein as "DNA40981-1234".

Figure 314 shows the amino acid sequence (SEQ ID NO:501) derived from the coding sequence of SEQ ID NO:500 shown in Figure 313.

Figure 315 shows a nucleotide sequence (SEQ ID NO:502) of a native sequence PRO363 cDNA, wherein SEQ ID NO:502 is a clone designated herein as "DNA45419-1252".

Figure 316 shows the amino acid sequence (SEQ ID NO:503) derived from the coding sequence of SEQ ID NO:502 shown in Figure 315.

Figure 317 shows a nucleotide sequence (SEQ ID NO:504) of a native sequence PRO5723 cDNA, wherein SEQ ID NO:504 is a clone designated herein as "DNA82361".

Figure 318 shows the amino acid sequence (SEQ ID NO:505) derived from the coding sequence of SEQ ID NO:504 shown in Figure 317.

Figure 319 shows a nucleotide sequence (SEQ ID NO:506) of a native sequence PRO3301 cDNA, wherein SEQ ID NO:506 is a clone designated herein as "DNA88002".

Figure 320 shows the amino acid sequence (SEQ ID NO:507) derived from the coding sequence of SEQ ID NO:506 shown in Figure 319.

Figure 321 shows a nucleotide sequence (SEQ ID NO:508) of a native sequence PRO9940 cDNA, wherein SEQ ID NO:508 is a clone designated herein as "DNA92282".

Figure 322 shows the amino acid sequence (SEQ ID NO:509) derived from the coding sequence of SEQ ID NO:508 shown in Figure 321.

Figure 323 shows a nucleotide sequence (SEQ ID NO:510) of a native sequence PRO9828 cDNA, wherein SEQ ID NO:510 is a clone designated herein as "DNA142238-2768".

Figure 324 shows the amino acid sequence (SEQ ID NO:511) derived from the coding sequence of SEQ ID NO:510 shown in Figure 323.

Figure 325 shows a nucleotide sequence (SEQ ID NO:512) of a native sequence PRO7170 cDNA, wherein SEQ ID NO:512 is a clone designated herein as "DNA108722-2743".

Figure 326 shows the amino acid sequence (SEQ ID NO:513) derived from the coding sequence of SEQ ID NO:512 shown in Figure 325.

Figure 327 shows a nucleotide sequence (SEQ ID NO:514) of a native sequence PRO361 cDNA, wherein SEQ ID NO:514 is a clone designated herein as "DNA45410-1250".

Figure 328 shows the amino acid sequence (SEQ ID NO:515) derived from the coding sequence of SEQ ID NO:514 shown in Figure 327.

Figure 329 shows a nucleotide sequence (SEQ ID NO:516) of a native sequence PRO846 cDNA, wherein SEQ ID NO:516 is a clone designated herein as "DNA44196-1353".

Figure 330 shows the amino acid sequence (SEQ ID NO:517) derived from the coding sequence of SEQ ID NO:516 shown in Figure 329.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO

polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are comtemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, preferably at least about 81% amino acid sequence identity, more preferably at least about 82% amino acid sequence identity, more preferably at least about 83% amino acid sequence identity, more preferably at least about 84% amino acid sequence identity, more preferably at least about 85% amino acid sequence identity, more preferably at least about 86% amino acid sequence identity, more preferably at least about 87% amino acid sequence identity, more preferably at least about 88% amino acid sequence identity, more preferably at least about 89% amino acid sequence identity, more preferably at least about 90% amino acid sequence identity, more preferably at least about 91% amino acid sequence identity, more preferably at least about 92% amino acid sequence identity, more preferably at least about 93% amino acid sequence identity, more

preferably at least about 94% amino acid sequence identity, more preferably at least about 95% amino acid sequence identity, more preferably at least about 96% amino acid sequence identity, more preferably at least about 97% amino acid sequence identity, more preferably at least about 98% amino acid sequence identity and most preferably at least about 99% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, often at least about 20 amino acids in length, more often at least about 30 amino acids in length, more often at least about 40 amino acids in length, more often at least about 50 amino acids in length, more often at least about 60 amino acids in length, more often at least about 70 amino acids in length, more often at least about 80 amino acids in length, more often at least about 90 amino acids in length, more often at least about 100 amino acids in length, more often at least about 150 amino acids in length, more often at least about 200 amino acids in length, more often at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y